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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,420	07/12/2001	Ann Bethea Begovich	RPA1003	3564

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,420	BEGOVICH ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1.Claims 1-3, 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for identifying human subjects having an increased likelihood of having multiple sclerosis or type I Diabetes wherein the methods comprise detecting the presence of an A allele at position 883 of the TCF-1 gene of SEQ ID NO: 1 as indicative of an increased likelihood of the individual having multiple sclerosis or type I diabetes, and methods for identifying human subjects having an increased likelihood of having an increased IgE response wherein the methods comprise detecting the presence of an C allele at position 883 of the TCF-1 gene of SEQ ID NO: 1 as indicative of an increased likelihood of the individual having increased IgE response, does not reasonably provide enablement for methods for characterizing an individual as possessing any factor which leads to an increased tendency for responding to an antigen with a Th1 or Th2 response or for characterizing an individual as possessing a factor contributing to an increased risk of a Th1 or Th2-mediated disease wherein the methods comprise detecting the presence of an polymorphism at position 883 of the TCF-1 gene of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or

unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn broadly to methods for characterizing an individual as possessing any factor which leads to an increased tendency for responding to an antigen with a Th1 or Th2 response or for characterizing an individual as possessing a factor contributing to an increased risk of a Th1 or Th2-mediated disease wherein the methods comprise detecting the presence of a polymorphism at position 883 of the TCF-1 gene of SEQ ID NO: 1. In particular, the Th-2 mediated disease is asthma or atopy and the Th1-mediated disease is multiple sclerosis or type 1 diabetes. The specification (see Example 7 and page 49) teaches that, in a Spanish population, the presence of an A allele at position 883 of the TCF-1 gene (as defined in SEQ ID NO: 1) was found to be associated with an increased occurrence of MS. The specification (Example 5 and page 42) teaches that, in a Caucasian population, the presence of an A allele at position 883 of the TCF-1 gene was found to be associated with type I diabetes. Further, the specification (Example 8 and pages 58-59) teaches that, in a combined population, the presence of a C allele at position 883 of the TCF-1 gene was found to be associated with increased IgE response. Accordingly, the specification has enabled methods for identifying human subjects having an increased likelihood of having multiple sclerosis or type I diabetes wherein the methods comprise detecting the presence of an A allele at position 883 of the TCF-1 gene of SEQ ID NO: 1 and methods for identifying human subjects having an increased likelihood of having an increased IgE response wherein the methods comprise detecting the presence of an C allele at

position 883 of the TCF-1 gene of SEQ ID NO: 1. While the specification also discloses that TCF-1 is one component of a system which controls T cell differentiation, the specification has not taught that the 883 polymorphism itself is associated with T cell differentiation and has not established a universal association between the 883 polymorphism and factors associated with an increased tendency for responding to an antigen with a Th1 or Th2 response or factors associated with increased risk of any Th1 or Th2-mediated disease. The association of the 883A allele with multiple sclerosis and type I diabetes is not sufficient to indicate that the 883A allele is associated with all Th1 mediated diseases or with factors associated with increased tendency to respond to an antigen with a Th1 response. Similarly, the association of the 883C allele with IgE responsiveness is not sufficient to indicate that the 883C allele is associated with all Th2 mediated diseases or with factors associated with increased tendency to respond to an antigen with a Th2 response. It is highly unpredictable as to whether the 883 polymorphism is associated with "factors" contributing to an increased tendency for responding to an antigen with a Th1 or Th2 response or with all Th1 and Th2 mediated diseases. The unpredictability in the art is highlighted by the teachings in the specification. In Example 6 (pages 44-45), Applicants teach that the 883A polymorphism may not be associated with type I diabetes in all ethnic groups, particularly in Mexican American populations. On page 45, Applicants report that "The above results, although not statistically significant, may suggest a trend that is opposite to the trend observed in the larger study presented in the previous example". That is, the specification at page 45 teaches that the results obtained in the Mexican American population studied indicate

that the 883C allele, rather than the 883A, allele is associated with type I diabetes. Applicants further state that "The results in the previous example indicate that the effect of the TCF-1 genotype is small, and it may require large study populations to unambiguously determine the effect". These teachings suggest that the findings obtained with one sample population may not be extrapolated to other sample populations and/or that the effect of the TCF-1 polymorphism is so minor, that large, varied populations are required to detect an effect. With respect to asthma and atopy, the specification (page 58) discloses that "The British data appear to be consistent with an absence of genetic effects contributing to the presence of asthma or atopy." The specification further states that "The pattern for the Australian data is similar to that for the British data. The data appear to be consistent with an absence of genetic effects contributing to the presence or absence of asthma, wheeze and atopy" (see page 59). The specification does not provide sufficient guidance as to how to apply the disclosed assays of detecting the 883 polymorphism to methods for characterizing individuals in any ethnic group as possessing a factor contributing to an increased tendency for responding to an antigen with a Th1 or Th2 response or as having a factor contributing to an increased risk of a Th-1 and Th-2 mediated diseases. Additionally, the specification does not exemplify any methods in which asthma or atopy or any Th1 or Th2-mediated response, other than multiple sclerosis, type I diabetes or IgE responsiveness, is diagnosed by detecting the presence of the polymorphism at position 883 of the TCF-1 gene. As stated in *Vaek* (20 USPQ2d 1438), the "specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis

added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art". With respect to the present invention, one cannot readily anticipate that the 883 polymorphism will be associated with other factors which contribute to "an increased tendency for responding to an antigen with a Th1 or Th2 response" or with other Th1 or Th2-mediated diseases. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

2. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6 are indefinite over the recitation of "**said** gene sequence is provided as SEQ ID NO: 1". This phrase lacks proper antecedent basis and therefore it is not clear as to what gene sequence is being referred to. Furthermore, it is unclear as to what is intended to be meant by the

sequence being "provided as" SEQ ID NO: 1. This rejection may be overcome by amendment of the claim to recite, for example, "wherein said TCF-1 gene consists of the sequence of SEQ ID NO: 1".

Claims 7-11 are indefinite for failing to recite a final process step which agrees back with the preamble. Claims 7-9 are drawn to a method for determining the genotype of a sample. However, the claims recite a final step of "detecting if hybridization occurs, which indicates the presence of said allele". The claims do not clearly indicate how detecting the presence of "said allele" results in determining the genotype of the sample. Similarly, claims 10 and 11 are drawn to a method for determining the genotype of a sample, yet, the claims recite a final step of "detecting if amplification occurs, which indicates the presence of said allele". Again, the claims do not clearly indicate how detecting the presence of "said allele" results in determining the genotype of the sample. Further, the claims are indefinite and confusing over the recitations of "said allele" because the claims refer to an "A allele" and to a "C allele" and it is unclear as to whether "said allele" refers to either the A allele or the C allele or to both the A and C alleles.

Claims 8 and 9 are indefinite over the recitation of "segment of region of said nucleic acid encompassing said region is amplified" because it is unclear as to what each recitation of "region" is referring to and it is unclear as to whether the "region of said nucleic acid" is the same as "said region" and if both or either are the same as the "region encompassing position 883".

Claims 12, 13, 15 and 16 are indefinite over the recitation of "substantially complementary". Substantially is relative terminology and this term is not clearly defined in the specification. See In re Nehrenberg (CCPA) 126 U.S.P.Q. 383. Therefore, it is not clear as to what level of complementarity would be encompassed by "substantially complementary".

Claims 12-17 are indefinite over the recitation of "either strand of SEQ ID NO: 1". SEQ ID NO: 1 is actually only the sequence of a single strand of DNA and therefore it is not clear as to what constitutes "either strand".

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by van de Wetering (Journal of Biological Chemistry (1992) 267: 8530-8536; reference "AB").

van de Wetering teaches an isolated TCF-1 nucleic acid which comprises a region of the sequence of SEQ ID NO: 1, wherein the region is of a length greater than 35 nucleotides and includes position 883 of the TCF-1 gene (see Figure 1 of van de Wetering). For example, the sequence of van de Wetering comprises the sequence of:

5'-GAGACCGTCTACTCCGCCTTCAATCTGCTCATGCATTACCCACCCCCCTCG-3',

which is a region of SEQ ID NO: 1 of at least 35 nucleotides which contains "the polymorphic site at nucleotide position 883". Furthermore, it is noted that the nucleic acid of van de

Wetering contains additional sequences which comprise "the polymorphic site". Since the claims broadly recite that the surrounding nucleotides may be "substantially complementary" to SEQ ID NO: 1, and thereby may share any level of sequence identity with SEQ ID NO: 1, and because claim 12 does not recite a length limitation for the region, the identity of the nucleotides surrounding "the polymorphic site" (i.e. a "C" nucleotide") have been so defined broadly so as to encompass any nucleic acid of at least 10-35 nucleotides that includes a "C".

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over van der Wetering (reference "AB").

van de Wetering teaches an isolated TCF-1 nucleic acid which comprises a region of the sequence of SEQ ID NO: 1, wherein the region is of a length greater than 35 nucleotides and includes position 883 of the TCF-1 gene (see Figure 1 of van de Wetering). For example, the sequence of van de Wetering comprises the sequence of:

5'-GAGACCGTCTACTCCGCCTTCAATCTGCTCATGCATTACCCACCCCCCTCG-3',

which is a region of SEQ ID NO: 1 of at least 35 nucleotides which contains "the polymorphic site at nucleotide position 883". Furthermore, it is noted that the nucleic acid of van de Wetering contains additional sequences which comprise "the polymorphic site". Since the claims broadly recite that the surrounding nucleotides may be "substantially complementary" to SEQ ID NO: 1, and thereby may share any level of sequence identity with SEQ ID NO: 1, and because claim 12 does not recite a length limitation for the region, the identity of the nucleotides surrounding "the polymorphic site" (i.e. a "C" nucleotide") have been so defined broadly so as to encompass any nucleic acid of at least 10-35 nucleotides that includes a "C". van de Wetering teaches that the TCF-1 gene was cloned and sequences in order to study the control of TCF-1 expression and how TCF-1 effects T cell differentiation. van der Wetering does not teach packaging the TCF-1 nucleic acid in a kit.

However, reagent kits for performing detection methods were conventional in the field of molecular biology at the time the invention was made. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged

the TCF-1 nucleic acids in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to detect and further characterize the TCF-1 gene

5. Claims 1-11 are allowable over the prior art because the prior art does not teach a polymorphism at position 883 of the TCF-1 gene of SEQ ID NO: 1. Accordingly, the prior art does not teach or suggest determining the genotype of the TCF-1 gene at position 883 by contacting a sample nucleic acid with an allele-specific primer or probe and determining the identity of the nucleotide at position 883 of the TCF-1 gene. Furthermore, the prior art does not teach or suggest the claimed methods of diagnosis which require detection of the polymorphism at position 883 of the TCF-1 gene of SEQ ID NO: 1. With respect to claims 14 and 17, the prior art does not teach or suggest the specifically claimed primers and probes of SEQ ID NO: 4, 5, 8 and 9.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Pauline Farrier whose telephone number is (703) 305-3550.

Carla Myers
July 17, 2002

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER